The effect of zoledronic acid on the markers for remodelled bone in Paget’s disease

Summary

Background: The arrival of the bisphosphonates signified an advance in the treatment of Pagets’s disease of bone (PDB), but agents which are more efficacious and easier to use are needed to improve the complement of treatments. Zoledronic acid, a bisphosphonate administered in the form of a single intravenous perfusion, could satisfy these requirements.

Method: We administered a perfusion of 15 minutes in duration of 5 mg of zoledronic acid to patients with PDB. The principal criterion for evaluating efficacy was the rate of therapeutic response at 6 months and 12 months, defined as a normalisation of the levels of alkaline phosphatase (AP), of amino-terminal propeptide of procollagen type 1 (P1NP), as markers for formation, and of carboxy-terminal telopeptide of collagen type 1 (CTX) as marker for resorption. We also evaluated the response of AP, CTx and P1NP at 18 months and 24 months.

Results: At 6 months and 12 months all the patients who received zoledronic acid presented a therapeutic response with normalisation of levels of AP, P1NP and CTx. The response was maintained at 18 and 24 months, although only one patient showed raised levels of AP at 24 months, coinciding with an elevation of hepatic gamma-glutamyl transpeptidase.

Conclusions: A single perfusion of zoledronic acid produces a rapid, complete and sustained response in PDB.

Key words: Paget’s disease of bone, Zoledronic acid, Bone markers.
Introduction
Paget's disease of bone (PDB) is a process with an unknown cause which affects approximately 3% of the population over 55 years of age. It is the second most frequent cause of bone metabolism disease after osteoporosis. Around 2% of the United States population over 60 years of age, and between 6% and 7% of older people in western Europe suffer from PDB. It is characterised by being a localised affection of remodelled bone which starts with an increase in bone resorption mediated by the osteoclasts, with a later compensatory increase in the formation of new bone. The result is a disorganised mosaic pattern in the trabecular and cortical bone. This structural change produces bone which is increased in size, less compact, more vascular and more susceptible to deformation and fracture than normal bone.

To assess the activity of the disease and to supervise the response to treatment biochemical markers for bone turnover are used. Although a viral origin of the disease, or the existence of immunological changes, have been invoked, the true aetiology of this disease is not known, and we cannot count on an appropriate therapy for its cure and must use pharmacological agents which suppress the activity of the pagetic osteoclasts, essentially the antiresorptives. On the one hand, the group of calcitonins, of salmon, of human, or of eel, administered principally intramuscularly or subcutaneously and, in some cases, intranasally, and on the other, the group of biphosphonates.

The indications for treatment and the choice of a therapeutic agent for the treatment of PDB even now continues to be debated. Improving the symptoms and preventing future complications should be the logical objectives of treatment for PDB. It has been clearly demonstrated that the suppression of the pagetic process by any of the agents can reduce certain symptoms, such as bone pains due to locally increased heat, headache due to the affection of the skull, secondary lumbago due to pagetic changes in vertebrae, and a number of neural compression syndromes, in the majority of those patients. Pain due to secondary arthropathy in the spine, hip, knee or arm does not usually respond to antipagetic treatment. Although it is possible that osteolitic lesions can partially recuperate, deformities of the extremities do not improve after treatment, and deafness is almost impossible to reduce, although some studies certainly suggest a slow improvement in auditory ability after treatment.

In asymptomatic patients, the indications for treatment are less clear. There is no proof that a substantial reduction in the biochemical indices of the activities of PDB might prevent future complications. However, Meunier et al. have observed a conversion to a normal pattern of layered bone in bone biopsies after suppression of pagetic activity. We also know that the active disease if untreated, may lead to the maintenance of a persistent degree of abnormal remodelled bone over many years, and develop complications in the bone or surrounding tissue. Therefore, the presence of moderate asymptomatic activity, such as FA two or three times above the upper limit of normality, is an indication for treatment. The biphosphonates, the treatment most used for PDB, often normalise the biochemical markers for bone turnover, achieves the substitution of chaotic fibrous bone for normal layered bone, and can also reduce bone pain. The oral biphosphonates which are used nowadays should be administered daily, orally, over a period of two to six months; in addition, the patients need to fast before and after the treatment due to the low bioavailability of these drugs, and to stay upright for 30 minutes after their administration, in order to reduce the high risk of gastrointestinal complications. Another, intravenous, biphosphonate, pamidronate, is also used, which is a little impractical for patients because it is usually administered in a number of slow intravenous perfusions, which last some hours, and which require multiple visits. The development of drugs which are more comfortable to use, more efficacious and with a more prolonged effect could resolve these problems. Among the biphosphonates which have been used in clinical trials, zoledronic acid was highly efficacious in preclinical models. Administered as a single perfusion lasting 15 minutes, its effects on the bone mineral density in postmenopausal women are similar to those achieved with 12 months of treatment with oral biphosphonates. A recent study has shown its efficacy in the treatment of PDB.

This medicine offers the possibility of significant improvements in terms of its ease of use and therapeutic accomplishments, which, along with its higher efficacy, could increase the rate of response and the duration of periods of remission.

In this study we have assessed the effects of zoledronic acid on the biochemical indices of the disease's activity.

Method
Patients
18 patients (12 males and 6 females) in the Polyclinic for Bone Metabolism Diseases in our hospital, older than 30 years of age and diagnosed with PDB through traditional methods (bone gammagraphy and biochemical markers for bone turnover), were studied. The average age of the patients was 74 years (with a range of 50-91 years), two patients (11%) presented a monostotic form, and 16 patients (88%) corresponded to a poliostotic form. The exclusion criteria were the existence of primary hyperparathyroidism; data indicative of liver or kidney disease; history of uveitis, iritis or diabetic nephropathy or retinopathy; and the use of treatments for PDB in the preceding 180 days.

Treatment
The patients received an intravenous perfusion of 5 mg of zoledronic acid over a period of 15 minutes. In the background they were administered orally 1g of calcium a day and between 400 and 1,000 UI of vitamin D a day.
Assessment criteria
At the baseline, and at 6 and 12 months, levels of were determined of creatinine and FA using an autoanalyser (modular Roche DDPP), and of P1NP aminoterminal propeptide (ELISA) as another marker for formation, and CTx telopeptide (ELISA) as marker for resorption. In six patients an assessment was carried out at 18 months and in four at 24 months. All except three patients had raised levels of FA (average: 192 UI/l, normal, up to 129 UI/l). All had raised levels of P1NP (168.7 ug/l, normal, up to 62 ug/l. In 16 patients the values of CTx were raised (average: 0.895 ng/ml, normal, up to 0.548 ng/ml).

The principal criterion for the assessment of the therapeutic response was the proportion of patients in whom were obtained a normalisation of levels of FA, P1NP and CTx.

Results
At 6 months and 12 months from the infusion of zoledronic acid, a normalisation of the levels of FA, P1NP and CTx was observed in 100% of the patients. At 6 months a reduction was observed in FA of 64%, in CTx, of 78.4%, and in P1NP, of 83.2%. The response at 12 months was similar, maintaining normality in these parameters in 100% of the patients. The reduction in FA was 62%, in CTx, 75.4% and in P1NP, 83.5% (Figures 1, 2 and 3). The response to the infusion of zoldronic acid was a significant reduction in blood levels of biochemical markers, although higher for P1NP and lower for CTx.

The number of patients studied at 18 and 24 months was small (6 and 4 patients), but it was observed that the levels of FA, CTx and P1NP stayed normal in all of them, except in one case in which a discrete elevation in the level of FA was produced, which coincided with an increase in hepatic GGTP. The reduction in FA was 64.21% at 18 months and 52.05% at 24 months, that of CTx was 81.9% at 18 months and 75.2 at 24 months and P1PNP was 75.0% at 18 months and 80.7% at 24 months.

All the patients had an acceptable clinical response without significant secondary effects, although some presented light flu-like symptoms, without other significant biochemical changes, except a patient who developed hypocalcaemia after the infusion.

Discussion
The study corroborated the safety and efficacy of a therapy in a single dose for PDB, already demonstrated in an earlier study'1. A single perfusion of 5 mg of zoledronic acid, administered over a period of 15 minutes, produces changes in various biochemical markers for bone activity.

Alendronate, taken orally, produces a reduction in concentrations of FA of 73% to 79% at 6 months12,13, with normalisation of this index in 48-63% of patients. Other trials with risedronate have shown a reduction in concentrations of FA of 69% to 77% at 6 months, with normalisation in its blood levels in up to 73% of patients14,15. Tiludronate reduces the concentrations of FA by 49-59% at 6 months, with normalisation of levels in 11-44% of patients16. Ibandronate administered intravenously reduces levels of FA by 70% after one or two doses17.
When PDB is treated with biphosphonates, the duration of the remission depends to a great extent on the nadir reached by the metabolic turnover of the bone, for which reason it is probable that the interval between treatments is very prolonged with this drug.

This fact could bring benefits for patients both in reference to the ease of treatment and the risk of long term complications, such as degenerative arthropathy.

In an earlier study, zoledronic acid had shown a normalisation of FA of 88.6% at 6 months after infusion. In our case, the normalisation was 100%, with a reduction in levels of 64.21%. The normalisation of levels of P1NP and CTx were also 100%, with a reduction in P1NP of 83.2%, higher than that achieved for FA, probably due to the fact that blood concentration of P1NP is a more specific index for osteoblast activity.

The bone resorption, assessed using the blood concentration of CTx, showed reductions of a similar magnitude, although somewhat less, as P1NP. Reid et al. found a higher reduction in CTx than in P1NP in the first weeks after the infusion, consistent with the fact that the osteoclasts are the principal target for the biphosphonates.

In the aforementioned study, in the follow up after the trial (median: 190 days), only one of the 113 patients treated with zoledronic acid presented a loss in the therapeutic response. In our series, 100% of the patients maintained their normal levels of FA, P1NP and CTx at 12, 18 and 24 months, although one patient showed a slight increase in FA at 24 months coinciding with an increase in hepatic GGT. These data are in accord with the series of Hosking et al., who studied the follow up to 2 years of the patients included in the group of Reid et al., in whom the response achieved at 6 and 12 months was maintained.

Our results confirm the efficacy of zoledronic acid in patients with PDB and add information to the data available by observing that prolonged remissions can be obtained.

The magnitude and duration of the effect of zoledronic acid are, probably, the result of its administration in a single dose, the great affinity of the drug with the minerals in the bone, and its powerful inhibition of the enzyme farnesyl diphosphate synthase. The persistence of its effect makes it especially appropriate for the treatment of PDB, in that the necessity of frequently repeating a treatment is a big clinical problem.

In order to achieve a reduction in the incidence and the seriousness of complications in the long term, a persistent normalisation in bone turnover over many years may be necessary, and this now appears to be a realistic possibility with the use of zoledronic acid.

The flu-like symptoms are frequent after the intravenous administration of aminobiphosphonates and have been noted in two thirds of patients treated with pamidronate for Paget’s disease.

Asymptomatic hypocalcaemia is frequent after the use of intravenous biphosphonates in patients with Paget’s disease and rarely require therapeutic intervention, although those patients with pre-existing hypocalcaemia or vitamin D deficiency should be treated before receiving these drugs.

Our results indicate that the use of calcium supplements is fundamental for reducing to the minimum the appearance of asymptomatic hypocalcaemia.

In conclusion, we have established that a single perfusion of zoledronic acid can achieve rapid and prolonged remission, obtaining an excellent biochemical response at 6 and 12 months, achieving normalisation of raised levels of the markers for remodelled bone, a normalisation which is maintained at 18 and 24 months.

The effect is maintained for up to two years after treatment. The long duration of the remission could give way to a more complete control of the activity of the disease than has been possible up until now.

P1NP is the marker which has the better response to the administration of this compound and may serve as the outstanding marker in the diagnosis and follow up to treatment of Paget’s disease.

Bibliography

12. O’Doherty DP, Gertz BJ, Tindale W, Sciberras TT, Kanis...